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Utilization of retrograded waxy maize starch gels as tablet matrix for controlled release of theophylline

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ABSTRACT

Theophylline tablets were prepared using waxy maize starch gels and the effect of retrogradation on the release of theophylline was investigated. Slurries of starch and theophylline were autoclaved in a polypropylene tablet mold and then stored at 4 °C or cycled at 4/30 °C for 8 days. By increasing the period of retrogradation at 4 °C the size of air cells in freeze-dried gels was decreased and the cell walls became thinner. Retrogradation reduced the pore size of the gels and hindered gel swelling in an amylase-containing dissolution medium. These effects became more significant with temperature cycles. The resistance to enzymatic erosion and decreased swelling by the retrogradation under 4/30 °C cycles resulted in a retarded release of theophylline. Thus, temperature-cycled retrogradation of a waxy maize starch gel provided a compact matrix structure that effectively retarded the drug release.

1. Introduction

Starch is commonly used as an excipient in tablets to control drug release. Hydrophilic polymers (Michailova, Titeva, Kotsilkova, Krusteva, & Minkov, 2001; Sanchez, Torrado, & Lastres, 1995) and emulsifiers (Conde-Petit & Escher, 1995) are often added to the starch-based tablets or the starch itself can be physically and/or chemically modified to further retard drug release. Starch modifications include chemical substitution (Pohja, Suihko, Vidgren, Paronen, & Ketolainen, 2004; Tuovinen, Peltonen, & Järvinen, 2003), crosslinking (Gluck-Hirsh & Kokini, 1997; Mulhbacher, Ispas-Szabo, Lenaerts, & Mateescu, 2001), pregelatinization (Michailova et al., 2001; Yoon, Kweon, & Lim, 2007), and retrogradation (Elfstrand, Eliasson, Jönsson, Reslow, & Wahlgren, 2006; Te Wierik, Eissens, Bergsma, Arends-Scholte, & Bolhuis, 1997; Trimnell, Shasha, & Otey, 1985).

During retrogradation, starch chains re-associate and recrystallize through inter/intramolecular hydrogen bonding and van der Waals forces thereby raising their enzymatic resistance (Tako, 1996). The amount and polymorph of the starch crystals depend on the retrogradation conditions (Elfstrand et al., 2006; Trimnell et al., 1985; Te Wierik et al., 1997). The recrystallized starch gel usually contains B-type crystals (Marsh & Blanshard, 1988) that are characterized by hexagonal stacks of double helices (Collison, 1968; Hsein-Chih & Sarko, 1978; Imberty & Perez, 1988). The rate and degree of retrogradation and recrystallization of the starch largely depend on the temperature (Lu, Jane, & Keeling, 1997; Silverio, Fredriksson, Andersson, Eliasson, & Åman, 2000), and various attempts to influence the degree of recrystallization by modifying the temperature have been made (González-Soto, Mora-Escobedo, Hernández-Sánchez, Sánchez-Rivera, & Bello-Pérez, 2007; Jang & Pyun, 1997; Vandeputte, Vermeylen, Geeroms, & Delcour, 2003). Water is usually required for starch chains to have the mobility necessary for recrystallization (Farhat, Blanshard, & Mitchell, 2000), yet excess water limits the association of the starch chains. Fifty to sixty percent water content is optimal for retrogradation, and common refrigeration (4 °C) is nearly ideal for starch crystallization (Baik, Kim, Cheon, Ha, & Kim, 1997). However, mild heating is often recommended for the propagation of starch crystallization.

In addition to the starch crystals, the characteristics of the amorphous matrix in a tablet can be an important factor in drug release. The gel network structure is determined mainly by the non-ordered matrix formation through starch chain associations. In the case of amylopectin, intermolecular double helices are formed by the association of the exterior starch chains. And although these associations do not develop into an ordered crystal structure they contribute the formation of non-ordered gel network (Cameron, Durani, & Donald, 1994; Gidley et al., 1995). Some homogeneous amorphous starch chain networks have been shown to be highly resistant to enzymatic hydrolysis and suitable for use as tablet matrix (Herman & Remon, 1989). Interestingly, the structure of the amorphous matrix in tablets is also dependent on the retrogradation conditions.

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The conventional method for tablet manufacture is direct compression of mixtures of drug and excipient. Therefore, in addition to the tablet components, the compressibility of the components is important. In the case of resistant starch (RS), despite its resistance to enzymatic erosion, its use as an agent for controlling drug release is limited because of the defects in compaction and gel formation (Yoon, 2007). To overcome the defects in compaction, glassy gels have been used as release matrices (Bajpai & Saxena, 2004). Because gels are readily formed without compaction, the problems associated with compressing mixtures of dry polymeric materials can be avoided. Currently, hydrogels are widely used as the basis for many oral drugs and patches (Eaimtrakarn et al., 2003; Valenta, Auner, & Loibl, 2005).

Theophylline was used as a model drug in this study. It has been widely used in various controlled release systems such as compressed tablets (Ceballos, Cirri, Mastrelli, Certi, & Mura, 2005), spray dried matrices (Asada, Takahashi, Okamoto, Tanino, & Danjo, 2004), and emulsions (Leadi Cole & Wateley, 1997). In addition, it has a good thermal stability (melting between 270 and 274), and almost constant solubility (1 g/120 ml) in a wide range of pH (pH 2 and 7.5), which are suitable properties for release tests. Having a narrow therapeutic range (10–20 μg/ml), however, the release control to maintain the optimal theophylline level is practically required (Mengozzi, Intorre, Bertini, Giorgi, & Soldani, 1998).

In this study, a hydrogel made of waxy maize starch (40% starch solids) was investigated as a tablet matrix for theophylline. The gel was stored at 4 °C or at cycled temperatures of 4/30 °C for 8 days. The effects of retrogradation on the starch crystallization, gel morphology, and the release of theophylline were examined.

2. Materials and methods

2.1. Materials

A commercial waxy maize starch was supplied by Samyang Genex Company (Seoul, Korea). Theophylline and porcine pancreatic α-amylase were purchased from Sigma–Aldrich Chemical Company (St. Louis, MO).

2.2. Preparation of retrograded gels

An aqueous slurry of waxy maize starch (40%, db) containing sodium azide (0.02%, a preservative) was heated in a water bath (70 °C) for 80 s to prevent the phase separation during autoclaving and then autoclaved (130 °C, 10 min) in a polypropylene cylinder container (14-mm diameter and 13-mm depth) to gelatinize starch slurry. The starch paste was sealed and retrograded by storage at 4 °C or in 4/30 °C cycles (2 days at each temperature) for up to 8 days. For the drug release test, theophylline was added to the starch paste (20%, w/w based on starch solids) prior to autoclaving.

2.3. Differential scanning calorimetry

Melting temperatures and enthalpy of the starch crystals in the retrograded gels were measured using a differential scanning calorimeter (DSC6100, Seiko Instruments, Chiba, Japan). A starch gel containing 3 mg of dry solids was placed in an aluminum pan (Seiko Instrument, Chiba, Japan) and distilled water was added to make the ratio of starch solids to water equal to 1:1.5. The pan was then sealed, equilibrated at room temperature for 1 h, and analyzed by heating from 17 to 130 °C at a rate of 5 °C/min. An empty pan was used as a reference and indium was used to calibrate the instrument.

2.4. Electron microscopy

The retrograded starch gels were freeze-dried and vertical sections of the gels were observed via a scanning electron microscopy (SEM) at an accelerating voltage of 20 kV (JSEM 5410LV System, JOEL, Japan).

2.5. Pore size distribution

Pore size distribution of the retrograded starch gels before and after enzymatic erosion was determined using a mercury (Hg) porosimeter (Micrometrics, Norcross, GA). The enzymatic erosion was carried out in a phosphate buffer solution (0.05 M, pH 6.8) containing pancreatic α-amylase (50 mg/l, 15,000 IU) while shaking at 100 rpm and 37 °C for 3 h. The gels were rapidly frozen by immersing in liquid nitrogen and freeze-dried. Non-wetting Hg was forced into the pores of the retrograded gel under pressure. Porosity (%) was determined by dividing the intrusion volume of Hg by the volume of the gel. Mean pore size was determined from the graph of percent maximum intrusion volume of Hg versus each pore diameter. Error ranges for the applied pressure and the intrusion volume were kept within 0.1% and 1%, respectively. Hg surface tension and contact angle were 485 dynes/cm and 140°, respectively. Maximum head pressure and Hg density were 4.6800 psi and 13.54 g/ml, respectively.

2.6. Swelling, erosion and drug release

Swelling, erosion, and drug release for the retrograded gels were tested using a USP dissolution tester (Woojoo Sci. Co., Korea). The starch gel tablet was stirred in a phosphate buffer solution (0.05 M, pH 6.8) containing pancreatic α-amylase (50 mg/l, 15,000 IU) at 100 rpm and 37 °C. Percents of swelling and erosion were calculated by measuring the tablet weights (db) before and after dissolution. For the drug release test, the amount of theophylline released into the buffer solution was measured by spectrophotometry at 268 nm (Yoon et al., 2007).

2.7. Statistical analysis

Significant differences between means were detected by the Duncan's multiple range test ($p < .05$). Statistical analysis was performed using the SAS software package (2001).

3. Results and discussion

3.1. Differential scanning calorimetry

The melting temperature and enthalpy of the crystals in the retrograded starch gels as measured by DSC are shown in Table 1. The temperature and period of retrogradation affected the melting characteristics of the starch crystals. As the storage time increased the melting temperatures and enthalpy values increased. It has been reported that retrogradation at cycled temperatures induces the formation of more homogeneous and stable gels than isothermal retrogradation (Silverio et al., 2000). Crystal nucleation in a starch gel is favored by refrigerated conditions, but crystal growth is usually facilitated with a temperature increase (30 °C in this study). Compared to the gels stored under isothermal conditions (4 °C), the gels stored at the cycled temperatures conditions (4/30 °C) had higher onset temperatures (T_o) and narrower melting range ($T_c - T_o$). However, the melting enthalpy values of the temperature-cycled gels were smaller than those of the isothermal gels. The increased onset temperature might indicate that the crystals formed by using the cycled temperatures had higher stability

Table 1
Melting temperatures and enthalpy of waxy maize starch retrograded at various conditions[a].

Storage temperature	Storage days	T_o (°C)	T_p (°C)	T_c (°C)	T_c-T_o (°C)	ΔH (J/g)
Native waxy maize starch						
4 °C	1	39.4^{c}	47.0^{e}	53.5^{d}	14.1^{ab}	2.16^{bc}
	2	39.7^{c}	46.3^{e}	54.0^{d}	14.3^{ab}	2.55^{ab}
	4	39.5^{c}	46.7^{e}	56.8^{bcd}	17.2^{a}	2.74^{ab}
	8	42.7^{b}	51.6^{bc}	58.9^{abc}	16.2^{a}	4.13^{a}
4/30 °C cycle	4	41.8^{bc}	50.6^{cd}	55.8^{bcd}	14.0^{ab}	1.91^{bcd}
	8	42.7^{b}	45.8^{e}	53.7^{d}	11.1^{bc}	1.94^{bcd}

[a] Results are means of three determinations. Values not sharing a common superscript within column differ significantly ($p < .05$).

than those formed at the isothermal retrogradation. However, the lower values of melting enthalpy suggested that overall crystallinity could be less when the cycled temperatures were used. It was possible that the helices of amylopectin side chains which had not transformed to starch crystals had been disrupted by increasing the temperature to 30 °C, resulting in the reduced levels of crystallinity.

3.2. Scanning electron microscopy (SEM)

The matrix structure inside the retrograded waxy corn starch gel was examined after lyophilization. Vertical sections inside the dried gels were observed by SEM (Fig. 1). The appearance of the matrix structure differed according to the retrogradation conditions. As the period of storage increased, the air cells in the sponge-like dry samples became smaller and the cell walls became thinner. As the retrogradation of a starch gel progresses, the starch chains associate and water clusters are formed. This process often leads to the contraction of the matrix and results in syneresis: a phase separation into starch-rich and starch-deficient regions (Miles, Morris, & Ring, 1984). Considering that the size of the air cells represents the size of the water clusters, the smaller-sized cells that we observed suggest that syneresis occurred during retrogradation, and the water loss resulted in smaller-sized water clusters.

The matrix structure of the starch gel retrograded at 4/30 °C differed from that retrograded at 4 °C. Unlike the isothermally retrograded gels, the temperature-cycled gels did not show discontinuous air cells. This result suggested that the water in the temperature-cycled gel matrix resided in the continuous phase, not as in separated water clusters. As mentioned, during the storage at 30 °C, some amylopectin helices might be transformed into amorphous although crystal propagation was facilitated. The structural changes induced by the warm storage at 30 °C might have induced the formation of a different type of matrix structure. More research is necessary to elucidate the mechanisms of gel matrix formation during retrogradation under temperature cycling.

3.3. Pore size distribution

When a compacted tablet is consumed, a gel layer is formed on the outer surface of the tablet by solvent penetration. The layer formation thus controls the rates of erosion and drug release. Lee and Yen (2000) reported that the pore size and pore distribution in the gel layer govern the initial swelling and drug release.

The porosity and pore size were influenced by the retrogradation conditions (Table 2). When the gels were retrograded at 4 °C, the storage period had little effect on the porosity and pore size. However, the temperature of retrogradation had a significant effect. Gels cycled at 4/30 °C had a significantly smaller pore size than that of the gels retrograded at 4 °C. It is possible that crystal propagation induced during the retrogradation at 30 °C made the gel matrix denser; thus, the reduced pore size would hinder swelling and drug release.

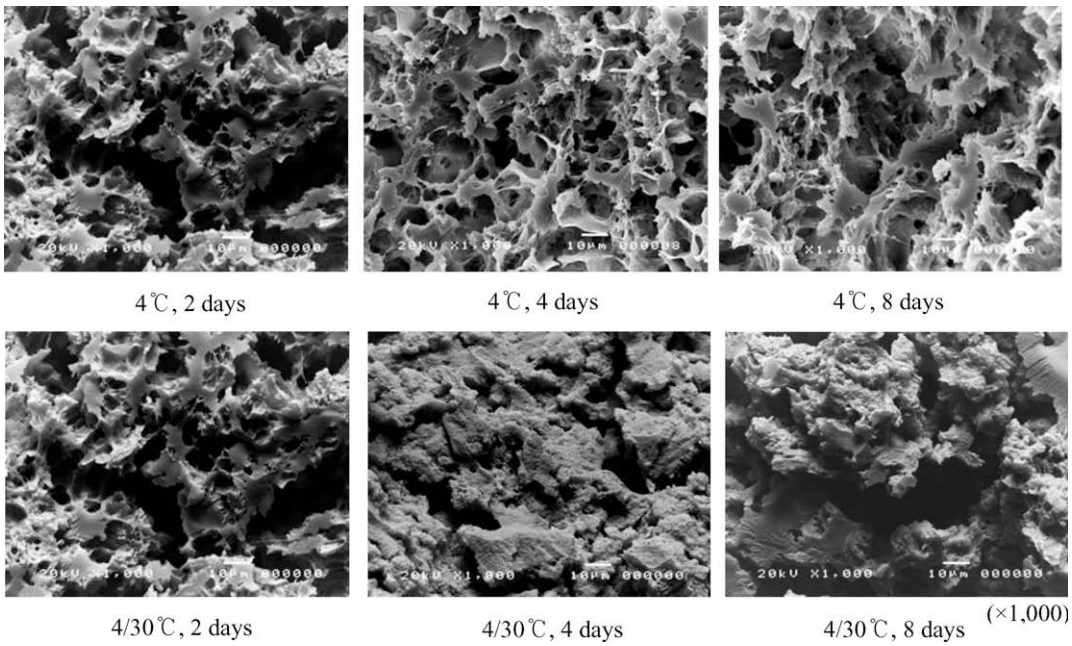

Fig. 1. Scanning electron micrographs (SEM) of vertical sections of waxy maize starch gels retrograded at various conditions (1000×).

Table 2
Porosity and average pore diameters of waxy corn starch gels retrograded at various conditions[a].

Storage	Porosity (%) Enzymatic hydrolysis		Average pore diameter (μm) Enzymatic hydrolysis	
	Before	After	Before	After
4 °C, 1 day	56.4[ab]	55.9[b]	0.25[c]	0.65[a]
4 °C, 8 days	55.3[b]	56.5[ab]	0.23[c]	0.54[b]
4/30 °C, 8 days	54.9[b]	59.4[a]	0.15[d]	0.20[cd]

[a] Results are means of three determinations. Values not sharing a common superscript within column differ significantly ($p < .05$).

After enzymatic erosion in a dissolution medium for 3 h, the average pore size increased significantly (Table 2). Compared to the gels stored at 4 °C, the gels retrograded under temperature cycling displayed less changes in pore size. This result agrees with the previous report in which retrogradation at cycled temperatures (4/30 °C) induced more homogeneous and stable structures (Silverio et al., 2000).

Tablets prepared by compacting starch powders displayed much greater increases in pore size under the same enzymatic erosion conditions (Yoon et al., 2007) as compared to the retrograded gels (data not shown). These data indicate that the tablets prepared with the retrograded starch gels have greater enzymatic resistance than do compacted tablets of starch powders and suggest that the intra- and intermolecular hydrogen bonds of the amylopectin chains induced by retrogradation contributed to the formation of a stable, enzyme-resistant gel network.

3.4. Tablet erosion and drug release

As solvent penetrates into tablet matrix, the tablet gradually erodes and releases drug into the dissolution medium. During retrogradation, the starch chain association stabilizes the gel matrix, as reported by Ratnayake, Hoover, and Warkentin (2002). The increased gel stability imparted by retrogradation was proved by the reduced swelling as shown in Fig. 2. Solvent penetration into the gel matrix was hindered by retrogradation, as supported by the associated decrease in pore size (Table 2). The gels retrograded under temperature cycling swelled to a lesser degree than did the gels retrograded at 4 °C. These data indicate that the crystal propagation and changes in amorphous matrix that occurred during temperature-cycled retrogradation provided the more compact gel structure. The SEM images (Fig. 1) and the average pore size data attest to the differences in gel rigidity.

Ordinarily, erosion of the gel layer on the tablet's surface induces drug release. In this study, the erosion rate was measured and correlated with the drug release. However, the erosion of all the samples tested was very low, less than 10% (Fig. 3). Unlike conventional tablets formed by direct compaction with starch powders, the network formed during retrogradation, either amorphous or crystalline, by the association of the outer chains of amylopectin (Miles, Morris, & Ring, 1985; Ring et al., 1987) resulted in a gel system with good rigidity and high enzyme resistance (Eerlingnen, Jacobs, & Delcour, 1994). The increases in porosity and pore size during the enzymatic erosion (α-amylase) that were relatively less than those found with the tablets of starch powders (Yoon et al., 2007) agreed with the erosion data. It has been reported that a waxy starch consisting of amylopectin had a greater resistance to α-amylase erosion than did a normal starch containing amylose, due to the (1 → 6) branch linkages (Ring, Gee, Whittam, Orford, & Johnson, 1988; Zhang & Oates, 1999). The retrogradation of amylopectin is much slower than that of amylose, which contributes to the formation of a more enzyme-resistant structure (Fredriksson et al., 2000). In our study, the tablets of retrograded starch gels maintained their integrity in the dissolution medium during the testing period (data not shown), showing their potential resistance to the physical impact of gastrointestinal duct.

Retrogradation period had little effect on drug release whereas retrogradation temperature imparted significant differences (Fig. 4). Considering that the crystal formation increased as the storage period increased (Table 1), the rate of drug release was

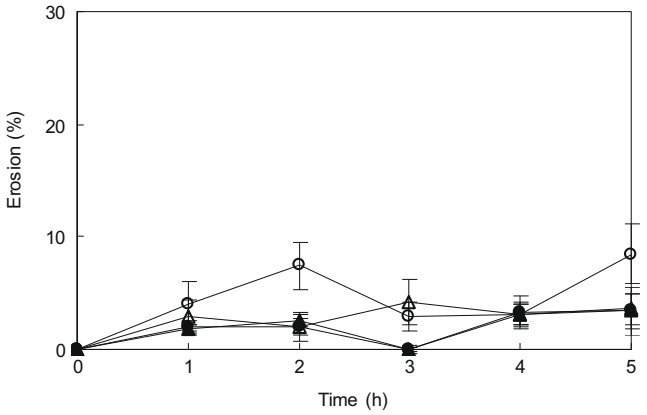

Fig. 3. Erosion of waxy maize starch gels retrograded at various conditions. (▲) 4 °C, 4 days, (●) 4 °C, 8 days, (△) 4/30 °C, 4 days, (○) 4/30 °C, 8 days, ($n = 3$).

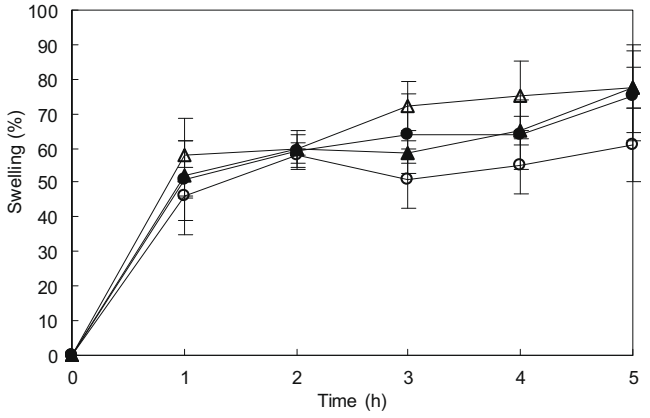

Fig. 2. Swelling of waxy maize starch gels retrograded at various conditions. (▲) 4 °C, 4 days, (●) 4 °C, 8 days, (△) 4/30 °C, 4 days, (○) 4/30 °C, 8 days, ($n = 3$).

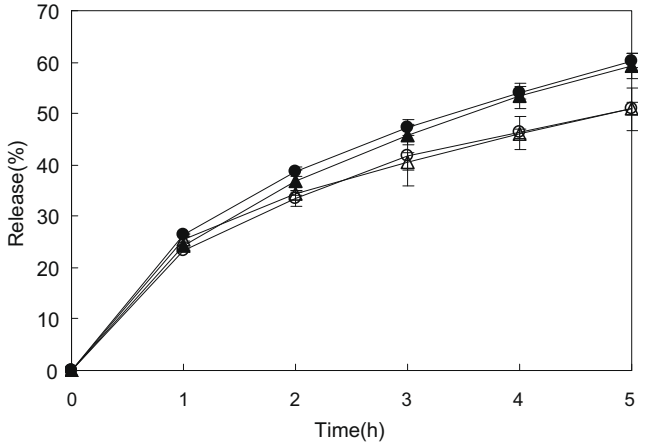

Fig. 4. Drug release of waxy maize starch gels retrograded at various conditions. (▲) 4 °C, 4 days, (●) 4 °C, 8 days, (△) 4/30 °C, 4 days, (○) 4/30 °C, 8 days, ($n = 3$).

hardly affected by the amount of crystals present in the starch gels. The gels retrograded at 4/30 °C showed slower releases of theophylline than those retrograded at 4 °C, indicating that the gel matrix formed by temperature cycling was more effective in retarding the drug release.

As supported by the narrow melting range ($T_c - T_o$) (Table 1), using temperature cycling (4/30 °C) for nucleation and propagation might promote the formation of a more homogeneous and stable crystalline structure by inducing changes in the amorphous network. Because the amount of crystals had little effect on the release behavior, the amorphous network formed during temperature cycling must have affected drug release. Different amorphous networks might result in morphologically different gel matrices (Fig. 1). Thus, retrogradation at cycled temperatures provided a gel matrix of amorphous and crystalline regions in which theophylline resided with greater stability.

4. Conclusions

Waxy starch gels can be used as tablet matrices having a good stability and controlled release of drugs such as theophylline. Retrogradation, either isothermally or by temperature cycling, influenced the morphology and drug release characteristics of the gels. Retrogradation made the gel denser, less swollen, and more resistant to digestive enzymes. These effects were enhanced when the gels were retrograded under temperature cycling (4/30 °C) versus under isothermal conditions (4 °C). Therefore, retrogradation at cycled temperatures retarded the release of theophylline by forming a stable amorphous network.

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